Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study

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Summary

Background **In-vitro and animal experiments have shown that the cyclo-oxygenase 2 inhibitor celecoxib can reduce formation of neointima within stents. We aimed to test whether celecoxib has similar effects in a clinical setting.**

Methods **In a randomised two-centre trial, we enrolled 274 patients who had angina pectoris or a positive stress test and who had native coronary artery lesions for which implantation of paclitaxel-eluting stents was feasible. All patients were given aspirin (100 mg daily) and clopidogrel (75 mg daily). 136 patients were randomly assigned to receive celecoxib (400 mg before the intervention, and 200 mg twice daily for 6 months after the procedure). The primary endpoint was late luminal loss on quantitative coronary angiography at 6 months after the intervention. Secondary endpoints were cardiac death, non-fatal myocardial infarction, and revascularisation of the target lesion. Analysis was done on a modified intention-to-treat basis. This study is registered with ClinicalTrials.gov, number NCT00292721.**

Findings **At 6 months, mean in-stent late luminal loss was lower in the celecoxib group (0·49 mm, SD 0·47) than in the control group (0·75 mm, 0·60) (absolute difference 0·26 mm; 95% CI 0·12–0·40). Frequency of secondary outcomes at 6 months was also lower in the celecoxib group, mainly because of a reduced need for revascularisation of the target lesion.**

Interpretation **These data suggest that the adjunctive use of celecoxib for 6 months after stent implantation in patients with coronary artery disease is safe and can reduce the need for revascularisation of the target lesion.**

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See **Comment** page 541

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Introduction

Drug-eluting stents can reduce neointimal hyperplasia in some coronary artery lesions.[1,2] However, restenosis is still a problem in practice, where patients and their lesions are complex.[3,4] Additionally, there are concerns about long-term thrombotic complications after implantation of drug-eluting stents.[5]

Celecoxib is a selective inhibitor of cyclo-oxygenase 2 (COX-2) that is commonly used as an anti-inflammatory agent. However, it also has antiproliferative, proapoptotic, and antitumour effects.[6–9] We have shown[10] that, through inhibition of the Akt-glycogen synthase kinase signalling axis, celecoxib inhibits proliferation of vascular smooth muscle cells and increases apoptosis of these cells in vitro, and inhibits neointimal hyperplasia after angioplasty in vivo. Wang and colleagues[11] also showed that celecoxib inhibits expression of monocyte chemoattractant protein 1 and activity of matrix metalloproteinase 2, and thus reduces formation of neointima after stenting.

Despite possible favourable effects on the vasculature, concern has been raised about the safety of celecoxib in terms of thrombosis, because selective COX-2 inhibitors can theoretically cause an unopposed excess of thromboxane A_2. Another COX-2 inhibitor, rofecoxib, was withdrawn from the market because of concerns that it increases risk of cardiovascular events.[12] Whether celecoxib has such an effect remains unclear, although two meta-analyses have shown that celecoxib does not increase the risk of cardiovascular events.[13,14] The hypothesis that celecoxib, through its antiproliferative and antirestenotic effects, might decrease the rate of restenosis and need for repeat procedures has not been tested. The aim of the Effect of Celecoxib on Restenosis after Coronary Angioplasty with Taxus stent (COREA-TAXUS) trial was to assess the efficacy of celecoxib in reducing neointimal hyperplasia in patients with coronary implantation of a paclitaxel-eluting stent (PES—in this study, the Taxus stent from Boston Scientific Corporation, Natick, MA, USA).

Methods

Patients

The COREA-TAXUS trial was a prospective, open-label randomised trial based at two centres in South Korea: the Seoul National University Hospital and the Seoul National University Bundang Hospital. Patients were enrolled between September, 2004, and March, 2006. Men and women were eligible if they were 18–75 years of age, had angina pectoris or a positive stress test, and had native coronary artery lesions for which PES implantation was feasible. Reasons for exclusion were: ST-elevation myocardial infarction; disease of the left main coronary artery; hepatic dysfunction; renal dysfunction (serum creatinine ≥177 μmol/L); severe congestive heart failure (New York Heart Association

classification >2); left-ventricular ejection fraction of less than 30%; haemodynamically unstable condition; uncorrected haematological disease; definite thrombus; contraindication to or history of allergy to aspirin, clopidogrel, or celecoxib; or expected survival of less than 2 years because of other medical conditions. Patients already taking warfarin, any COX-2 inhibitor, or any non-steroidal anti-inflammatory drugs were also excluded. All patients gave written informed consent and the institutional review boards at both centres approved this study.

Procedures

All patients were given aspirin and clopidogrel before coronary intervention. Aspirin (100 mg daily) was taken indefinitely and clopidogrel (75 mg daily) was taken for at least 6 months. Patients were randomly assigned to the celecoxib or control group in computer-generated blocks of six patients. Randomisation codes were provided by the research nurse a few minutes before the coronary intervention. This was an open-label study and a placebo was not used. Patients in the celecoxib group were given 400 mg celecoxib in the few minutes between receipt of the randomisation code and the start of the intervention, and 200 mg twice daily for the next 6 months. To investigate the effect of celecoxib in a representative population, patients who had PES implantation in lesions other than the target vessel were included. For patients who had PES implants in several vessels, the operator declared the target lesion before the intervention and decided the order of treatment. Coronary intervention followed standard techniques. Predilatation, post-stent adjunctive balloon inflation, and use of a glycoprotein IIb/IIIa inhibitor were all at the operators' discretion. Blood samples were taken immediately before and 1 month after stent implantation. Blood concentrations of high-sensitivity C-reactive protein (hs-CRP) were measured before stent implantation, and at 24 h and 1 month after the procedure.

Clinical follow-up visits were scheduled for 1 month after coronary intervention and every 2 months thereafter. Medical records were reviewed by investigators and by a study nurse; the nurse and physicians also asked patients about potential outcome or adverse events and drug compliance at each visit.

Coronary angiograms were obtained before and after the intervention within a single session, and 6 months after the procedure. Glyceryl trinitrate (100–200 μg) was administered into the coronary artery before each angiogram. The angiograms after the procedure and at 6 months were taken to show the same views as the baseline angiogram. Quantitative coronary angiography (QCA) was done by two independent angiographers who were not aware of the patients' celecoxib status and analysis was done with Quantcor QCA, version 4.0. Correlation coefficients for minimum lumen diameter were 0·922 (2·88±2·46% error) between observers and 0·972 (1·40±1·78%) within observers.

The contrast-filled tip of the catheter was used for calibration. Angiographic variables obtained were absolute lesion length, reference vessel diameter, minimum lumen diameter, percentage diameter stenosis, and late luminal loss (the difference between the minimum lumen diameter after the procedure and at 6-month follow-up). Restenosis was defined as more than 50% stenosis in the target lesion in the follow-up angiogram. Measurements were obtained for both the stented segment (in-stent) and margins 5 mm proximal and distal to the stent (in-segment). Lesion morphology was defined according to the guidelines of the American College of Cardiology and American Heart Association.[15]

The primary endpoint was the in-stent late luminal loss assessed by QCA at 6-month follow-up. Secondary endpoints were cardiac death, myocardial infarction, and need for revascularisation of the target lesion, at 6 months and yearly for 5 years after coronary intervention. All deaths were regarded as cardiovascular unless there was documented evidence of a clear non-cardiovascular cause. Myocardial infarction was defined as the presence of at least two of the following: ischaemic symptoms; concentrations of cardiac enzymes (creatine kinase and its MB isoenzyme, CK-MB) at least twice their upper normal limits; and

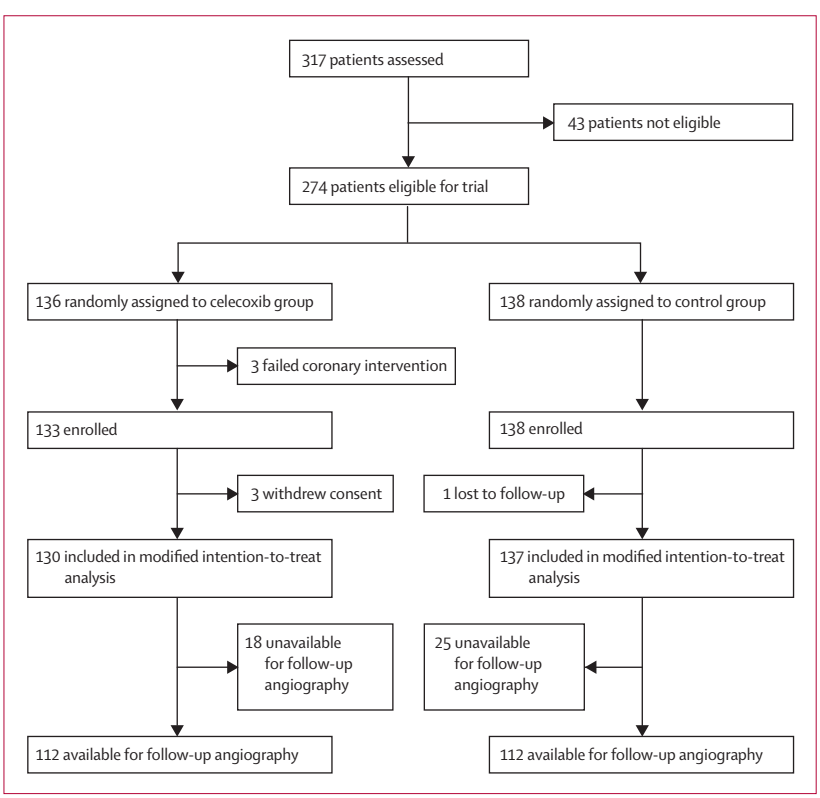

Figure 1: **Trial profile**

new electrocardiographic changes compatible with myocardial infarction. Periprocedural myocardial infarction was defined as an increase of CK-MB concentrations to more than three times the normal upper limit. Serum concentrations of CK-MB were measured 4 h and 8 h after stent implantation, and thereafter in patients with high CK-MB concentrations. Clinically driven target lesion revascularisation was defined as revascularisation done in lesions with 50–70% diameter stenosis that was related to ischaemic symptoms, objective signs, or both, or as revascularisation done in lesions with 70% or more diameter stenosis, even in the absence of ischaemic symptoms or signs.[16]

Statistical analysis

On the basis of the previous TAXUS trials (TAXUS I, II, and IV),[2,17,18] the in-stent late loss of PES was estimated to be 0·30 mm (SD 0·46). The COREA-TAXUS trial was designed to have 80% power to detect an expected 50% reduction in late loss after PES implantation with celecoxib, with a two-sided α level of 0·05. 208 patients were needed to detect this difference. Presuming an angiographic follow-up rate of 80%, we planned to enrol 260 patients. To adjust for the adherence to angiographic follow-up of less than 80%, we increased the sample size to 274 patients.

Analyses were on a modified intention-to-treat basis. We compared continuous variables using the Student's *t* test, and we analysed categorical variables using the χ^2 test or Fisher's exact test where appropriate. The Mann-Whitney U test was used to compare non-normally distributed data, such as hs-CRP concentrations. Serial changes of angiographic measurements were compared by use of a repeated measures ANOVA test with the Bonferroni correction. Event-free survival was analysed from the time of stent implantation to the first event according to the Kaplan-Meier method, and the difference was evaluated by log-rank test. STATA version 9.2 was used for all statistical analyses, and $p<0·05$ was considered statistically significant. This study is registered with ClinicalTrials.gov, number NCT00292721.

Role of the funding source

Neither the Innovative Research Institute for Cell Therapy nor the Korea Health 21 R&D Project, Ministry of Health & Welfare had involvement in study design, in collection, analysis, or interpretation of data, or in writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Table 1 shows baseline clinical, angiographic, and procedural characteristics of the 271 patients who entered the study. No characteristics differed between the two groups. Before enrolment, statins, β blockers, and either angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers were used by 55 (40%), 69 (50%), and 55 (40%) patients in the control group, and by 58 (44%), 81 (61%), and 36 (27%) patients in the celecoxib group, respectively. At discharge, statins were used by 101 patients (74%) in the control group and 95 patients (71%) in the celecoxib group.

	Control (n=138)	Celecoxib (n=133)
Patients' characteristics		
Mean (SD) age (years)	64·2 (55·0–73·4)	62·6 (53·5–71·7)
Male	91 (66%)	89 (67%)
Diabetes	42 (30%)	49 (37%)
Hyperlipidaemia	103 (75%)	89 (67%)
Hypertension	91 (66%)	90 (68%)
Current smoker	28 (20%)	24 (18%)
Previous myocardial infarction	8 (6%)	5 (4%)
Previous revascularisation	18 (13%)	16 (12%)
Diagnosis*		
Stable angina pectoris	80 (58%)	87 (65%)
Unstable angina	36 (26%)	32 (24%)
Lesion and procedural characteristics		
Lesion locations		
Left anterior descending CA	74 (54%)	72 (54%)
Left circumflex artery	33 (24%)	31 (23%)
Right CA	31 (22%)	30 (23%)
Type B2/C lesion†	118 (86%)	116 (87%)
Type C lesion†	67 (49%)	69 (52%)
Total occlusion	16 (12%)	13 (10%)
Bifurcation lesion	23 (17%)	27 (20%)
Moderate to heavy calcification	28 (20%)	26 (20%)
Glycoprotein IIb/IIIa inhibitor	4 (3%)	1 (1%)
Mean (SD) number of stents per lesion	1·2 (0·5)	1·2 (0·4)
Mean (SD) stent diameter (mm)	3·1 (0·3)	3·1 (0·3)
Mean (SD) stent length per lesion (mm)	30·6 (14·8)	29·7 (14·2)
Adjunctive balloon dilatation	108 (78%)	113 (85%)
Mean (SD) maximum inflation pressure, overall (kPa)	1371 (338)	1398 (339)

Data are number (%) or mean (SD). CA=coronary artery. *Other diagnoses were atypical symptom, silent ischaemia, non-ST segment elevation myocardial infarction, and old myocardial infarction. †American College of Cardiology and American Heart Association criteria.

Table 1: **Baseline clinical, angiographic, and procedural characteristics**

267 patients were included in the modified intention-to-treat analysis. Periprocedural myocardial infarction occurred in 20 patients (15%) in the control group and 18 (14%) in the celecoxib group (p=0·85). During 1 month of follow-up, there was one sudden cardiac death in the control group and one non-fatal myocardial infarction due to stent thrombosis in the celecoxib group.

Blood sample analyses were available for 123 control-group patients and 124 celecoxib-group patients (table 2). The remaining 20 patients who were included in the modified intention-to-treat analysis

	Control (n=123)	Celecoxib (n=124)
Baseline		
Systolic BP (mm Hg)	135·7 (24·7)	133·9 (24·4)
Diastolic BP (mm Hg)	80·0 (11·6)	80·4 (11·8)
Total cholesterol (mmol/L)	4·7 (1·0)	4·7 (1·1)
LDL cholesterol (mmol/L)	2·8 (0·8)	2·7 (0·9)
HDL cholesterol (mmol/L)	1·2 (0·3)	1·1 (0·3)
Haemoglobin (g/L)	135 (15)	144 (91)
Creatinine (μmol/L)	94·7 (17·2)	95·0 (18·5)
hs-CRP (mg/L)	3·2 (8·0)	2·9 (5·6)
At 1 month		
Systolic BP (mm Hg)	126·9 (19·5)	130·8 (19·5)
Diastolic BP (mm Hg)	74·6 (10·2)	75·8 (10·5)
Total cholesterol (mmol/L)	4·2 (0·9)	4·1 (1·0)
LDL cholesterol (mmol/L)	2·4 (0·9)	2·2 (0·8)
HDL cholesterol (mmol/L)	1·2 (0·3)	1·2 (0·3)
Haemoglobin (g/L)	136 (17)	136 (17)
Creatinine (μmol/L)	97·4 (16·0)	98·7 (23·1)
hs-CRP (mg/L)	2·3 (7·2)	2·4 (6·6)

Data are mean (SD). BP=blood pressure. LDL=low-density lipoprotein. HDL=high-density lipoprotein. hs-CRP=high-sensitivity C-reactive protein.

Table 2: **Changes in blood pressure and blood samples**

were not able to provide blood at the 1-month follow-up, but did take part in other follow-up. Blood pressure and blood sample values were similar in the two groups at baseline and at 1 month. Mean hs-CRP concentrations did not differ between the celecoxib and control groups at baseline (table 2, p=0·81), 24 h after the procedure (12·2 [12·4] *vs* 11·0 [10·8] mg/L, p=0·41), or 1 month after the procedure (table 2, p=0·93). In patients with silent ischaemia or stable angina, the difference in hs-CRP concentrations between baseline and 24 h after intervention was lower in the celecoxib group than in the control group (6·4 [7·5] *vs* 9·5 [10·1] mg/L, p=0·01).

Clinical outcomes were analysed in 267 patients (figure 1). 82% of patients in the control group and 86% of patients in the celecoxib group (p=0·33) were available for follow-up angiography. Table 3 shows QCA results at baseline, just after the coronary intervention, and at 6-month follow-up. Baseline QCA measurements did not differ between the two groups. Mean in-stent late loss, the primary endpoint of this study, was smaller in the celecoxib group than in the control group (table 3; 0·26 mm absolute reduction, 95% CI 0·12–0·40; 35% relative reduction, p<0·0001). Figure 2 shows the cumulative percentage of minimum lumen diameter before, just after, and 6 months after the procedure. The mean diameter changed over time within each group (p<0·0001 for all comparisons), and the nature of these changes differed between the groups (p=0·001). In-segment late loss was lower in the celecoxib group than the control group (table 3, p=0·001). Restenosis rate was also significantly lower in the celecoxib group than in the control group (in-stent p=0·007; in-segment p=0·001). The pattern of restenosis did not differ between the celecoxib and control groups (focal restenosis: 41% [14/34] *vs* 29% [4/14], p=0·5).

When all 315 lesions treated by PES (152 lesions in the control group and 163 in the celecoxib group) were analysed, in-stent late loss was 0·51 mm (0·48) in the celecoxib group and 0·67 mm (0·59) in the control group (absolute reduction 0·15 mm, 95% CI 0·03–0·27; 24% relative reduction, p=0·01). In-segment late loss was also lower in the celecoxib group than in the control group (0·36 [0·48] *vs* 0·51 [0·55] mm; absolute reduction 0·14 mm, 0·03–0·26; p=0·02).

The rate of adverse cardiac events within the first 6 months after stent implantation was lower in the celecoxib group than in the control group (table 4); this difference was mainly due to the lower need for revascularisation of the target lesion in the celecoxib group. The rate of clinically driven target lesion revascularisation was also lower in the celecoxib group. There was one non-fatal myocardial infarction due to stent thrombosis in the celecoxib group and one sudden cardiac death in the control group. The rate of adverse cardiac events was lower in the celecoxib group than in the control group for male patients, for patients younger than 65 years, and for patients without diabetes, with type C lesions, and with lesions in the left anterior

	Control (n=112)	Celecoxib (n=112)	p
Reference vessel diameter (mm)	2·85 (0·38)	2·88 (0·42)	0·51
Lesion length (mm)	27·5 (13·3)	26·9 (12·9)	0·75
Minimum lumen diameter in segment (mm)			
Before procedure	0·73 (0·45)	0·76 (0·41)	0·66
After procedure	2·25 (0·49)	2·20 (0·48)	0·40
At 6-month follow-up	1·69 (0·60)	1·87 (0·54)	0·018
Minimum lumen diameter in stent (mm)			
After procedure	2·54 (0·38)	2·51 (0·42)	0·52
At 6-month follow-up	1·79 (0·64)	2·02 (0·58)	0·006
Diameter of stenosis in segment (%)*			
Before procedure	74·2 (15·8)	73·6 (13·8)	0·77
After procedure	24·3 (12·2)	25·7 (12·3)	0·40
At 6-month follow-up	40·1 (18·8)	34·0 (15·4)	0·008
Diameter stenosis in stent (%)*			
After procedure	14·2 (8·0)	15·2 (9·3)	0·42
At 6-month follow-up	36·6 (20·1)	28·9 (16·6)	0·002
Binary restenosis at 6-month follow-up			
In stent	27 (24%)	12 (11%)	0·007
In segment	34 (30%)	14 (13%)	0·001
Late loss (mm)			
In stent	0·75 (0·60)	0·49 (0·47)	<0·0001
In segment	0·56 (0·57)	0·33 (0·43)	0·001

Data are mean (SD) or number (%). *% of reference vessel diameter lost to stenosis.

Table 3: **Angiographic results in 224 patients who underwent follow-up angiography**

descending coronary artery (figure 3). Survival free from cardiac events—defined as survival without myocardial infarction or need for revascularisation of the target lesion (mean follow-up 18·3 [6·2] months)—was higher in the celecoxib group for the duration of the follow-up (figure 4). Most events were revascularisation of the target lesion at the time of the follow-up angiography. After 6 months, all events were revascularisations of the target lesion, except for one non-cardiac death in the control group. There was no additional myocardial infarction or cardiac death during long-term follow-up in either group.

At 6 months, there was no difference in use of non-study drugs between the two groups. Mean duration of clopidogrel use was 350 days (182) in the control group and 323 days (170) in the celecoxib group (p=0·22). Statins, β blockers, and angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers were used by 103 (76%), 85 (63%), and 69 (51%) of 136 patients in the control group (1 patient had died) and by 95 (73%), 85 (65%), and 55 (42%) patients in the celecoxib group, respectively. Table 5 shows the reasons for discontinuation of celecoxib in the 18 patients (14% of that group) who stopped taking the drug before the designated 6 months. After discontinuation, renal function and gastrointestinal symptoms normalised in the patients who had stopped taking celecoxib because of renal dysfunction and gastrointestinal discomfort, respectively. There were no other serious side-effects in patients who continued to take celecoxib. Of the patients who discontinued celecoxib by their preference, nine did so within 1 month.

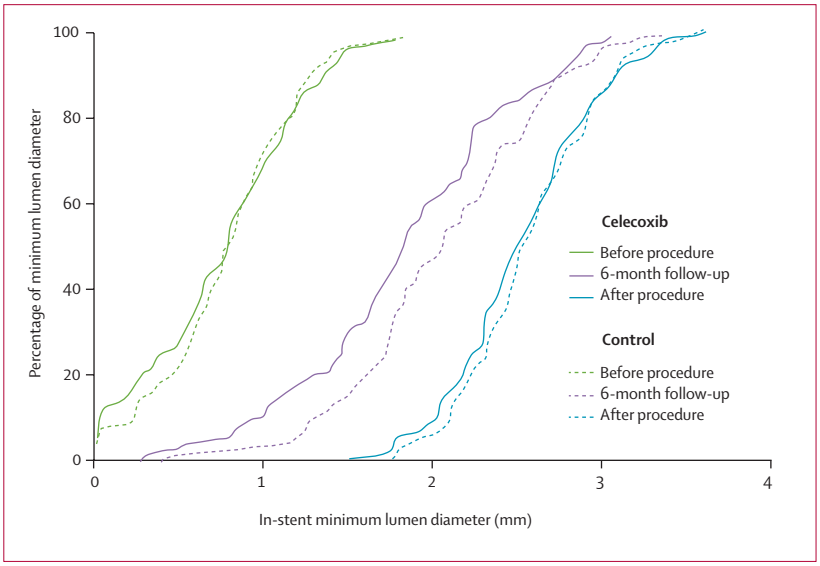

Figure 2: **Minimum lumen diameter before the procedure, after the procedure, and at 6-month follow-up**
In-stent minimum lumen diameter as measured by quantitative coronary angiography showed significant changes over time in each group (p<0·0001) and these serial changes were significantly different between the celecoxib and control groups (p=0·001).

Discussion

We have shown that adjunctive celecoxib treatment reduces late luminal loss at 6 months in patients with PES implantation without increasing frequency of thrombotic cardiac events. Administration of celecoxib for 6 months in patients with PES implantation reduced mean late loss by 35% at the end of this period. There was a 66% reduction in the relative risk of major adverse cardiac events, which was primarily due to a reduction in target lesion revascularisation. There was no difference in cardiac death and myocardial infarction between the two groups. The rate of clinically driven target lesion revascularisation was also significantly lower in the celecoxib group.

The mean late luminal loss in the control group at 6 months was higher than mean loss reported in other PES-related randomised controlled trials. Post-stent implantation residual stenosis was also higher in our study than in previous studies, perhaps owing to the lesion and procedural characteristics of the patients enrolled in this study. For example, the lesions were complex: half were type C, about a tenth were totally occluded, about a fifth had moderate to heavy calcification, and their mean stent length was almost 30 mm. In the TAXUS V trial,[19] in-stent late loss of PES in lesions with more than one stent was 0·60 mm (0·67), and in two studies of patients with long coronary artery lesions, in-stent late loss of PES was 0·78 mm (0·72) and 0·45 mm (0·55).[20,21] Moreover, late luminal loss after PES implantation in chronic total-occlusion lesions has been reported as 0·80 mm (0·8).[22] Thus, the unusually high late luminal loss at 6 months in the control group of this study should be viewed in the context of the complexity of the lesions in the patients who enrolled.

Although drug-eluting stents have shown excellent outcomes in clinical trials,[1,2] there seems to be room for short-term systemic therapy after stent implantation. In particular, the use of drug-eluting stents for non-standard off-label indications is increasing, and this practice is associated with increased risk of adverse cardiac events and repeat procedures.[23] As increasingly complex lesions are treated with drug-eluting stents, more patients will be at risk of restenosis, and

	Control (n=137)	Celecoxib (n=130)	Relative risk (95% CI)	p
Target lesion revascularisation	21 (15%)	7 (5%)	0·35 (0·15–0·80)	0·008
Clinically driven target lesion revascularisation	16 (12%)	6 (5%)	0·40 (0·16–0·98)	0·036
Non-fatal myocardial infarction	0 (0%)	1 (1%)	..	0·49
Cardiac death	1 (1%)	0 (0%)	..	1
Total	22 (16%)	7 (5%)	0·34 (0·15–0·76)	0·005

Data are number of patients (%) unless otherwise indicated.

Table 4: **Major adverse cardiac events within 6 months**

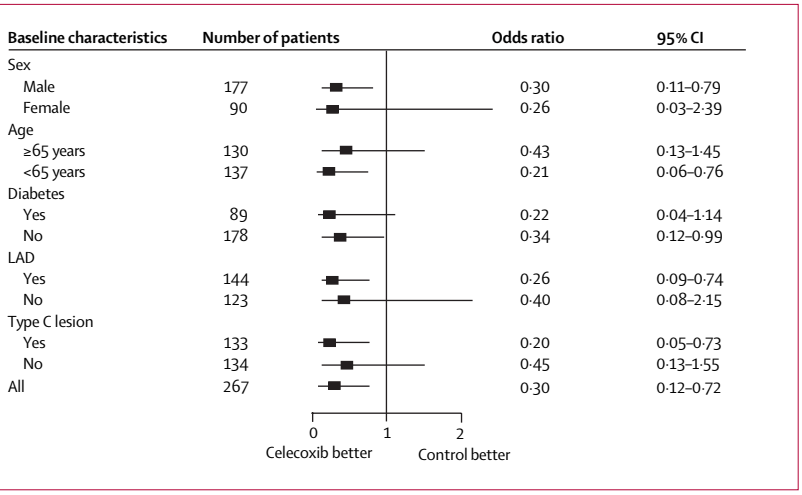

Figure 3: **Odds ratios for cardiac events at 6 months in patients grouped by baseline characteristics that are prognostic factors**
LAD=target lesion in the left anterior descending coronary artery.

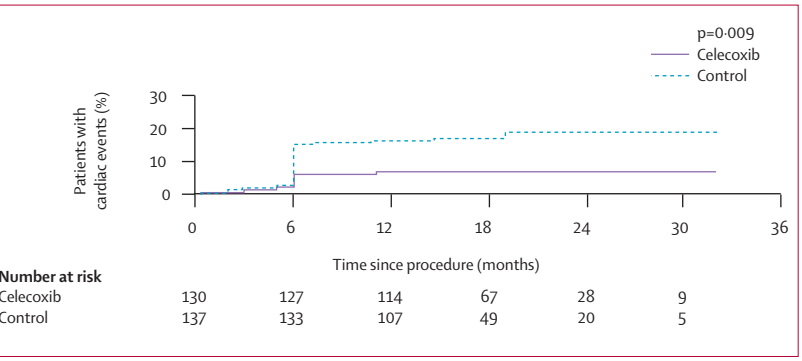

Figure 4: **Cardiac-event-free survival**
Cardiac events: cardiac death, non-fatal myocardial infarction, or revascularisation of the target lesion.

short-term systemic therapy might help to reduce this risk. Another therapeutic possibility for some patients might be use of bare-metal stents with short-term adjunctive systemic therapy to avoid the potential risk of long-term thrombotic events after implantation of drug-eluting stents. However, our study did not investigate this possibility. We should be careful not to make any clinical recommendations for the use of celecoxib on the basis of this study alone—such a recommendation will require double-blind studies in a much larger population with long-term follow-up.

The beneficial effect of celecoxib in reducing neointimal hyperplasia might be due to its antiproliferative and proapoptotic effects. Celecoxib has potent antitumour and antiproliferative effects in various cancer cell lines.[7–9] Celecoxib significantly reduces viability of vascular smooth muscle cells in vitro and inhibits neointimal hyperplasia in vivo.[10,11]

Another possible mechanism for the beneficial effects of celecoxib is the reduction of inflammation. Pelliccia and colleagues[24] showed that pretreatment with celecoxib for 7 days reduced procedural myocardial injury in stable angina patients who had elective coronary intervention. In the COREA-TAXUS study, celecoxib was given just before the coronary intervention and did not reduce the incidence of periprocedural myocardial infarction. The effect of COX-2 inhibitors on hs-CRP concentrations in patients with coronary artery disease is controversial.[25–27] In our study, celecoxib did not reduce hs-CRP concentrations, except for during the 24 h after stent implantation in patients with non-acute coronary syndrome. Bogaty and colleagues[25] showed that treatment with rofecoxib for 6 months significantly reduced hs-CRP concentrations in patients who had high concentrations, and Chenevard and colleagues[26] reported that celecoxib reduced hs-CRP concentrations and improved endothelial function in patients with severe coronary artery disease. However, Title and colleagues[27] reported that rofecoxib had no effect on endothelial function or on the concentrations of proteins that are indicators of inflammation. The reason for the conflicting results is unclear, but it might relate to the differences in baseline inflammatory activities, inflammatory stimuli, and drugs taken during follow-up.

We do not know whether the effect of celecoxib in reducing neointimal hyperplasia after stent implantation could be extended to other COX-2 inhibitors, but previous reports suggest not. Neiderberger and colleagues[28] showed that celecoxib, but not rofecoxib, inhibited the proliferation of vascular cells. Walter and colleagues[29] showed that sulphonamide COX-2 inhibitors, including celecoxib, had no effect on rates of low-density lipoprotein oxidation, whereas sulphone COX-2 inhibitors such as rofecoxib and etoricoxib seemed to increase this oxidation. Therefore, our results should not be extrapolated to other COX-2 inhibitors.

Despite the benefits of COX-2 inhibitors, caution was raised when rofecoxib was voluntarily withdrawn from the market by its manufacturer after the Adenomatous Polyp Prevention On Vioxx study.[12] Since publication of that study, there has been much controversy and intense debate about whether celecoxib increases the risk of adverse cardiac events. In the cardiovascular safety analysis of the Adenoma Prevention with Celecoxib trial,[30] the authors reported that the risk of cardiovascular

	Number of patients (n=18)
Reason for discontinuation	
Preference of the patient	13
Gastrointestinal discomfort	3
Transient renal dysfunction	2
Time to discontinuation	
≤1 month	12
1–3 months	5
>3 months	1

Table 5: **Drug discontinuation in the celecoxib group**

events in the celecoxib group was 2·6 times higher than in the placebo group. However, in large meta-analysis studies,[13,14] celecoxib, by contrast with rofecoxib, did not increase the risk of cardiovascular events. The effects of rofecoxib and celecoxib might differ because celecoxib is less selective for COX-2 than is rofecoxib, so the theoretical unopposed relative excess in thromboxane A_2 would not be as large with celecoxib. Furthermore, celecoxib does not inhibit the antiplatelet activity of aspirin,[31,32] and in both the Adenoma Prevention with Celecoxib trial[30] and the Prevention of Spontaneous Adenomatous Polyps trial,[33] celecoxib did not increase the risk of cardiovascular events in patients who were taking aspirin. Borgdorff and colleagues[34] reported that increased platelet aggregation by COX-2 inhibitors in the presence of an arterial stenosis could be prevented by low-dose clopidogrel. The follow-up duration of our study is short, so we cannot comment on the safety of administration of celecoxib over several years. But administration of celecoxib for 6 months does not seem to increase the risk of adverse cardiac events in the intermediate term when used with dual antiplatelet therapy. We will be interested to see the 2–5 year follow-up results of this cohort.

This study has some limitations. First, it was an open-label trial, not a placebo-controlled double-blind study. Therefore, the possibility of bias cannot be excluded, although the QCA was analysed by angiographers who were unaware of which study groups patients were in. Second, QCA was done in more than one laboratory, which might decrease the reliability of the findings. However, the variabilities within and between observers were very low, which suggests that reliability was not a source of differences in this study. Third, because the angiographic follow-up was at 6 months after the initial stent implantation, neointimal growth after this point was not assessed. However, the difference in the event-free survival between patients in the celecoxib and control groups, which was mostly due to differences in revascularisation of target lesions, was maintained after 6 months and for the duration of the follow-up. This finding suggests that the difference in late loss between the two groups did not change significantly after the angiographic follow-up at 6 months.

Contributors

B-KK and Y-SK contributed equally to this work. All authors contributed to the study design. H-JK, Y-SC, W-YC, T-JY, I-HC, D-JC, B-HO, and Y-BP participated in enrolment of patients, did invasive procedures, and contributed to clinical follow-up. D-AK, H-MY, J-WC, H-YL, and J-SP participated in data collection. B-KK, Y-SK, K-WP, J-YH, D-AK, H-MY, J-WC, H-YL, and J-SP participated in data analysis. B-KK, Y-SK, H-SK, H-JK, Y-SC, W-YC, T-JY, I-HC, D-JC, B-HO, and Y-BP contributed to data interpretation. B-KK, Y-SK, H-SK, K-WP, and J-YH contributed to writing of the paper, and all authors have seen and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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